III. Remarks

Claims 1-4 and 6 are presented for continued examination.

The Examiner maintains his assertion that the subject application is obvious over Haenggi *et al.* in view of Berglund. Specifically the Examiner argues that Haenggi *et al.* teach that tibolone decreases lipoprotein-A [Lp(A)] levels and that Lp(A) has been shown to be a strong risk factor for coronary heart disease. Further, the Examiner contends that this teaching, when taken in combination with Berglund, that the Examiner contends teaches that Lp(A) has been implicated with an increased risk of atherosclerosis renders the subject application obvious.

Applicants respectfully request reconsideration in light of this response. Applicants contend that the teachings of the prior art are being misconstrued and should be understood differently.

In the description of the subject application, starting on line 29 of page 2 to line 24 of page 3, it is explained that Tibolone has been the subject of studies assessing its long-term effects on lipid metabolism, since the compound (in addition to estrogenic activity) also has progestogenic activity and androgenic properties. These latter properties are associated with negative effects on lipoproteins, that is, causing 'a significant decrease in HDL-cholesterol and its major apolipoprotein A-1' (first paragraph of the

PAGE 5/8 * RCVD AT 12/30/2003 3:30:30 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:934 4305 * DURATION (mm-ss):02-18

Discussion on p.648 of Haenggi *et al.*). The studies indicated that the possibly beneficial decreasing effect of Tibolone on lipoprotein A serum levels 'might counterbalance, at least to some extent, the theoretical adverse effect on the other lipoprotein risk factors.' *i.e.*, those related to coronary heart disease (last paragraph of the Summary on page 645 of Haenggi *et al.*). Thus it can be concluded that Haenggi *et al.* merely teaches that with the administration of Tibolone, there is a possible balancing of positive and negative effects on coronary heart disease risk factors. Haenggi *et al.* does not teach or suggest the unexpectedly strong atheroprotective properties of Tibolone, that renders it useful in a method for inhibiting atherosclerosis.

According to Berglund, 'Lp (A) has been implicated with an increased risk of atherosclerosis and cardiovascular disease. Again, from this, the person skilled in the art can only conclude that with the administration of Tibolone, there is a possible balancing of positive and negative effects on atherosclerosis and cardiovascular disease risk factors. Berglund does not teach or suggest the unexpectedly strong atheroprotective properties of Tibolone which render it useful in a method for inhibiting atherosclerosis.

Applicants maintain that the properties of Tibolone, that underpins its utility in a method for inhibiting atherosclerosis, are not dealt with by either of the two cited prior art documents. Further, the subject application presents

PAGE 6/8 * RCVD AT 12/30/2003 3:30:30 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:934 4305 * DURATION (mm-ss):02-18

experimental data in support of this. As is explained in the specification of the present application (page 5, line 14 to page 6, line 8), Tibolone has an unexpected, significant and beneficial atheroprotective effect which is completely independent from its previously disclosed effects on plasma lipoproteins or lipoprotein A. The present inventors found that the compounds of formula I have a direct effect on cholesterol accumulation in the vessel wall. These effects on the vessel wall were observed in a generally accepted, relevant and validated atherosclerosis rabbit model. It is to be noted that in this rabbit model, lipoprotein A does not play a role at all, since it is not present in rabbit plasma. The unexpected and surprising effects of the present invention can be seen, for example, by comparing the data in Table III for Tibolone (i.e., Org OD 14) and estradiol (decanoate). Tibolone completely prevented cholesterol accumulation (i.e., expressed as cholesterol level) in the aortic arch whereas estradiol (decanoate) did not lead to a reduction in cholesterol accumulation. Furthermore, fatty streak formation in the aortic arch was completely prevented by treatment with Tibolone, whereas estradiol decanoate had only minor effects.

These unexpectedly strong atheroprotective effects of Tibolone could not have been derived from any of the prior art knowledge or teachings either alone or when taken together. Applicants therefore maintain that the claims of the present invention are not rendered obvious by the cited art. As was

PAGE 7/8 * RCVD AT 12/30/2003 3:30:30 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:934 4305 * DURATION (mm-ss):02-18

discussed in ***Interconnect Planning Corp. v. Feil***, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination. Here, as will be illustrated, Applicants' invention is not rendered obvious by the prior art.

IV. CONCLUSION

In light of this response, Applicants respectfully contend that the present invention is not obvious. Further, Applicants respectfully request that the Examiner contact Applicants' undersigned attorney to further the prosecution of the case. Please charge any required fees and credit any credits to deposit account 02-2334. Further, please charge the required fee for this request for continued examination.

Sincerely,

William P. Ramey, III
Reg. No. 44,295

Akzo Nobel Pharma Patent Department
Intervet, Inc.
P.O. box 318
405 State Street
Millsboro, DE 19966
(302) 933-4034 telephone
(302) 934-4305 facsimile

PAGE 8/8 * RCVD AT 12/30/2003 3:30:30 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:934 4305 * DURATION (mm-ss):02-18